

## **REMARKS**

### **Claim amendments**

Claim 2 has been amended to delete L<sup>1</sup> being isoindoline. Claims 3, 9, 10, 14, 17 and 18 have been deleted in that they do not further limit the claim on which they depend or they are redundant to a pending claim.

Claims 2, 4, 5, 12, 13-16, 25, 27, 34-37, 39, 40, 42 and 45-47 are now pending in the application. Applicants acknowledge that claims 34 and 35 are allowed.

### **Rejection of claim 36 under 35 USC §112, first paragraph**

As discussed in the previous response, the specification clearly provides an enabling disclosure to make and use the compounds recited in claim 36 in that they are illustrated in Examples 104-112 and their synthesis is described on pages 85-86.

The specification discloses how to administer these compounds to treat diseases on pages 16 -21, where it is stated the compounds may be administered orally, transdermally, parenterally, by injection, by inhalation or spray, or sublingually, rectally or vaginally in dosage unit formulations, and “one or more compounds may be present in association with one or more non-toxic pharmaceutically acceptable carriers and if desired other active ingredients.” Details regarding these forms of administration and the carriers are provided on pages 16-21.

The specification provides dosages for these compounds as “from 0.01 to 200 mg/Kg of total body weight,” for oral, injection, infusion, rectal, vaginal, topical and transdermal administration. The daily inhalation dosage regimen is disclosed as preferably from 0.01 to 10 mg/Kg of total body weight.

The specification clearly provides sufficient disclosure to enable the methods of claim 36 and provides more than it needs to in satisfying the requirements of 35USC §112, since the compounds listed in claim 36 were tested in an *in vitro* raf kinase assay and found to display IC<sub>50</sub>s of between 1 nM and 10 μM.

A cellular assay with human tumor cell lines HCT116 and DLD-1, to determine their effect on the proliferation of these cells is also provided. Given the extent of the disclosure provided, it would at most involve routine experimentation if any at all, for one of ordinary skill in the art to treat colorectal cancer with any one of the compounds recited in claim 36.

No evidence has been presented that this disclosure is insufficient to meet the enablement requirement under 35 USC §112, first paragraph, and no evidence has been presented to cast doubt on the teachings within the specification. Only unsupported allegations and conclusions regarding the art of cancer treatment are provided to support the rejection. Examples of these allegations are, “treating cancer is not predictable,” and “the specification has no data provided that would show that it indeed treats cancer.”

Without supporting evidence, the rejection is clearly deficient under controlling case law. As acknowledged on page 3 of the office action, the courts have placed the initial burden upon the PTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated; see, e.g., *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (CCPA 1971) (holding that how an enablement teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance.) The disclosure must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein. See *In re Marzocchi*, supra. No such evidence or reason for doubting Applicants’ disclosure has been provided. Only general statements and conclusions are made.

Additionally, “the [enablement] requirement is satisfied if, given what they [, those of ordinary skill in the art,] already know, the specification teaches those in the art enough that they can make and use the claimed invention without ‘undue experimentation.’” See *Amgen v Hoechst Marion Roussel*, 314 F.2d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003). Using the claimed compounds to treat colorectal cancer would be routine for those of ordinary skill in the art in view of applicant’s disclosure.

There is no requirement that applicants provide examples showing the treatment of colorectal cancer in patients to satisfy the statute. See, for example, *In re Angstadt*, 537 F.2d at 502-03, 190 USPQ 214 (CCPA 1976) (deciding that applicants “are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art”); *Uter v Higara*, 845 F.2d at 998-99, 6 USPQ2d 1714 (Fed. Cir. 1988) (holding that a specification may, within the meaning of Section 112, Para. 1, enable a broadly claimed invention without describing all species that claim encompasses). Instead, as discussed earlier, there is no requirement for any examples, see *In re Marzocchi*, supra and MPEP § 2164.02, which states, “compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed.”

Moreover, with respect to pharmaceutical inventions, an applicant is not required to test the claimed compounds in their final use (rigorous planned and executed clinical trials...” per the Examiner). The Federal Circuit in *In re Brana*, 51 F.3d 1560, 34 USPQ 1436 (Fed. Cir. 1995), stated that:

usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas.

It is alleged in the office action that “clinical correlations are generally lacking” for *in-vitro* assays and cell-cultured assays. This general observation, even if true, is insufficient to cast doubt on the teachings of this specification without evidence the assays disclosed in the application fail to correlate with clinical tests. It is acknowledged in the office action, “the examiner must also give reasons for a conclusion of lack of correlation for an *in-vitro* or *in vivo* animal model example.” However, no reasons for concluding a lack of correlation exists other than “unpredictability in the art is high.” No documents have been presented to support this

statement regarding unpredictability and even if true, the statement is not probative as to the presence or absence of correlation between *in-vitro* or *in vivo* animal models disclosed in the specification and clinical test results.

The PTO has failed to meet its burden of establishing that the disclosure does not enable one skilled in the art to make and use the compounds recited in claim 36 to treat colorectal cancer such that the rejection under 35 USC §112, first paragraph should be withdrawn.

**Rejection under 35 USC §103 in view of Atwal (US 5547966)**

Atwal (US Patent 5,547,966) provides no teaching, direction, or suggestion to prepare the compounds defined in claims 2, 4, 5, 12, 13-16, 25, 27, 34-37, 39, 40, 42 and 45-47, herein. As acknowledged in the office action, Atwal discloses aryl urea compounds which do not have the substituent "C(O)R<sub>x</sub>" on a remote phenyl group or pyridinyl group (corresponding to L<sup>1</sup> of formula I herein and corresponding to R<sup>1</sup> of formula I of Atwal).

Atwal does not disclose any compounds where R<sup>1</sup> is pyridinyl and does not disclose any compounds where R<sup>1</sup> is substituted phenyl. Only two compounds (Examples 14 and 15) have R<sup>1</sup> as phenyl and they are unsubstituted. Only one compound (compound 17) has a substituent consistent with "C(O)R<sub>x</sub>" herein and it is positioned on the "first phenyl group," not a remote ring, as is recognized in the office action. The specific compounds disclosed by Atwal are far removed from the compounds claimed herein and provide no guidance to incorporate any substituents on the phenyl or pyridinyl moieties of R<sup>1</sup>. Similarly, there is no guidance to position moieties consistent with "C(O)R<sub>x</sub>" at any location other than the ortho position of the "first phenyl."

The broad generic disclosure of Atwal also provides no direction to prepare any of the compounds claimed herein. Most significantly, the broad generic disclosure does not encompass compounds where R<sup>1</sup> is phenyl or pyridinyl substituted by "C(O)R<sub>x</sub>". Atwal defines R<sup>1</sup> as "alkyl, cycloalkyl, aryl, (aryl)alkyl, heterocyclo or (heterocyclo) alkyl" in column 1 lines 21-22.

At column 2, lines 28-50, Atwal further defines "aryl" as

a) phenyl, 1-naphthyl, 2-naphthyl, (unsubstituted),

b) phenyl, 1-naphthyl, 2-naphthyl mono-substituted with various groups such as (C<sub>1</sub>-C<sub>4</sub>) alkyl, (C<sub>1</sub>-C<sub>4</sub>) alkoxy, halo, cyano, hydroxyl, amino, (alkyl) amino, alkyl substituted amino, -NH-(C<sub>1</sub>-C<sub>4</sub>) alkyl, -N((C<sub>1</sub>-C<sub>4</sub>) alkyl)-CF<sub>3</sub>, -CHF<sub>2</sub>, substituted phenyl groups (see structures at col. 2, lines 35-41), -O-CH<sub>2</sub>-cycloalkyl or -S-CH<sub>2</sub>-cycloalkyl, and

c) phenyl, 1-naphthyl, 2-naphthyl, disubstituted with methyl, methoxy, methylthio, halo, -CF<sub>3</sub>, nitro, amino or -CHF<sub>2</sub>.

Atwal defines "heterocyclo" as including 2-, 3- and 4-pyridyl at col. 2, line 57. Atwal further defines the term "heterocyclo" at col. 3, lines 1-9, as including monocyclic and bicyclic rings wherein an available carbon atom is substituted with various groups such as (C<sub>1</sub>-C<sub>4</sub>) alkyl, (C<sub>1</sub>-C<sub>4</sub>) alkylthio, (C<sub>1</sub>-C<sub>4</sub>) alkoxy, halo, nitro, keto, cyano, hydroxy, amino, -NH-(C<sub>1</sub>-C<sub>4</sub>) alkyl, -N((C<sub>1</sub>-C<sub>4</sub>) alkyl)<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>2</sub>, and monocyclic and bicyclic rings wherein two or three available carbon atoms are substituted with methyl, methoxy, methylthio, halo, -CF<sub>3</sub>, nitro, hydroxy, amino or -OCF<sub>2</sub>.

The absence of any substituents for R<sup>1</sup> conforming to the structure of "C(O)R<sub>x</sub>" or chemical nature of "C(O)R<sub>x</sub>" from this broad disclosure is conspicuous. The absence of such a substituent is far more conspicuous when it is clear Atwal contemplated substituents consistent with "C(O)R<sub>x</sub>" on the first phenyl group. There is no basis for one skilled in the art to ignore the limitations on the substituents for R<sup>1</sup> taught by Atwal and modify either the compound of example 15 or 17 to arrive at any compound claimed herein.

The obviousness rejection based on structural similarity between the claimed compounds the compound of example 15 requires a preliminary finding that one of ordinary skill in the art would have selected the compound of example 15 as a lead compound for modification consistent with the holding in *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007). The preferred compounds defined at column 7 of Atwal encompass Examples 2, 3, 4, 5, 6, 10, 11, 12, 13, 14, 15, 17, and 18. No basis has been given for selecting example 15 as the lead, such that there is no support for the rejection under 35 USC§ 103.

In addition to the absence of evidence in selecting example 15 as the lead, no evidence has been presented showing one of ordinary skill in the art would have reason to attempt to modify the compound of Example 15 to make a compound claimed herein with a reasonable expectation that such a compound would retain the properties necessary for the treatment of ischemic conditions as disclosed by Atwal. There is no evidence the compounds claimed herein even have properties necessary for the treatment of ischemic conditions.

To maintain the rejection under 35 USC§ 103, it is necessary to show that the prior art would have suggested making the specific molecular modifications necessary to Example 15 of Atwal to achieve a compound within the scope of the claims herein. See *The Procter and Gamble Co. vs. TEVA Pharmaceuticals*, 2008-1404, 1405 1406, May 13, 2009.

While the compound of Example 15 may suggest a homolog, analog, or isomer to one skilled in the art because such compounds often have similar properties, it remains necessary to identify some reason that would have led a chemist to incorporate the group “C(O)R<sub>x</sub>” on a remote phenyl or pyridinyl group of R<sup>1</sup> although inconsistent with the teachings Atwal. See *The Procter and Gamble Co. vs. TEVA Pharmaceuticals*(supra). Applicants submit a modification inconsistent with the teachings of Atwal would not be routine and is unobvious, such that the rejection under 35 USC § 103 should be withdrawn.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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